

One-pot synthesis of 2,4,5-trisubstituted-1*H*-imidazoles promoted by nano-TiCl₄ · SiO₂: An experimental and theoretical study

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Nano-TiCl₄ · SiO₂ has been found to be an extremely efficient catalyst for the preparation of 2,4,5-trisubstituted imidazoles via three-component reactions of benzil, aldehydes and ammonium acetate under mild conditions. Nano-TiCl₄ · SiO₂ as a solid Lewis acid has been synthesized by reaction of nano-SiO₂ and TiCl₄. The structure characterization of this acid has been studied by XRD, SEM and TEM. This process was simple and environmentally benign with high to excellent yields. Furthermore, the catalyst could be recovered conveniently and reused for at least three times. Standard ab initio calculations have been carried out in order to identify the possible reaction mechanism.

Key words: 2,4,5-tri-substituted-1*H*-imidazoles, nano-TiCl₄ · SiO₂, benzil, solvent-free conditions, ab initio

INTRODUCTION

2,4,5-Triphenylimidazoles can be used as fungicides, herbicides, plant growth regulators and inhibitors of some kinases [1]. Meanwhile, substituted imidazoles are extensively used as antibacterial [2], antitumor [3], and glucagon receptors [4]. There are reported several methods for the synthesis of imidazoles such as the hetero-cope rearrangement [5], and four-component condensation of arylglyoxals, primary amines, carboxylic acids and isocyanides on Wang resin [6]. Recently, the synthesis of 2,4,5-trisubstituted imidazoles has been catalysed by ytterbium triflate [7], silicasulfuric acid [8], L-proline [9], ZrCl₄ [10], ionic liquid [11], Eu(OTf)₃ [12], InCl₃ · 3H₂O [13], DABCO [14], PEG-400 [15], silica supported Wells-Dawson heteropolyacid (WD/SiO₂) [16], zeolite HY [17], [EMIM]OAc [18], NaH₂PO₄ [19], *N*-methyl 2-pyrrolidone hydrogen sulfate [20], K10 [21], *n*-Bu₄NBr [22], (NH₄)₆Mo₇O₂₄ · 4H₂O [23], Nano-MgO [24], KH₂PO₄ [25] and InF₃ [26]. During the course of our studies towards

the development of new protocols for the synthesis of organic compounds, we wish to report a simple and efficient method for the synthesis of 2,4,5-triarylsubstituted imidazoles in the presence of nano-TiCl₄ · SiO₂. We have also used standard ab initio calculations in order to study the thermodynamics of two previously reported mechanisms of 2,4,5-trisubstituted imidazoles preparation from benzil, aldehyde and ammonium acetate.

EXPERIMENTAL

Chemicals

The chemicals were used from the Merck and Sigma-Aldrich Company without any additional purification.

Apparatus and software

The products were characterized by FT-IR (ATR), ¹H-NMR, and a comparison of their physical properties with those reported in the literature. FT-IR (ATR) spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-400 Avance) NMR was used to record the ¹H NMR spectra. The X-ray

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diffraction (XRD) patterns of materials were recorded by employing a Philips Xpert MPD diffractometer equipped with a Cu K α anode ($\lambda = 1.54 \text{ \AA}$) in the 2θ range from 10 to 80°. The SEM of nano particles determined with VEGA/TESCAN scanning electron microscope and a TEM photograph was prepared by a Leo 912AB OMEGA microscope.

Computational methods

The standard density functional theory calculations [27, 28] and ab initio molecular orbital theory [29, 30] were completed using the Gaussian 03 [31] software. Molecular geometries of all species were optimized at the B3LYP/6-31G(d) level of the theory [27, 28]. The nature of each stationary point was found via the B3LYP/6-31G(d) frequency calculations.

The optimized geometries have been used for further calculations. The MP2/G3MP2large level of the theory [32] has been used for calculation of relative free energies together with thermochemical data calculated at the recommended level of B3LYP/6-31G(d) [29]. The MP2/G3MP2large level of the theory has been selected considering the size of molecules and hardware limitations. Nonetheless, the results of this method are reliable for the calculation of relative energies [33].

General procedure for the synthesis of 2,4,5-trisubstituted imidazoles

A mixture of benzil (1 mmol), aldehyde (1 mmol), ammonium acetate (2 mmol) and nano-TiCl₄ · SiO₂ (0.04 g) was heated at 110 °C with good stirring. The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was cooled to room temperature and diluted with acetone. The catalyst was recovered by filtration and washed

with acetone (2 × 5 ml). By adding water to the filtrate, a milky to yellow solid was obtained. The dried solid was washed with hot *n*-hexane to obtain highly pure product. All the products were identified by comparison of their physical and spectral data with those of authentic samples.

2-(4-Isopropyl phenyl)-4,5-diphenyl-1*H*-imidazole (Table 3, entry 2)

FT-IR: (KBr) = 3029, 2961, 1602, 1490, 837, 765, 696 cm⁻¹.

¹H-NMR (500 MHz, DMSO-*d*₆): 12.60 (s, 1 H, N-H), 8.01 (d, ³*J* = 8.2 Hz, 2 H), 7.35 (d, ³*J* = 8.2 Hz, 2 H), 7.38–7.52 (m, 10 H), 2.94 (sep, ³*J* = 6.9 Hz, 1 H, C-H), 1.25 (d, ³*J* = 6.9 Hz, 6 H, 2CH₃) ppm. Elemental analysis. Found, %: C 85.03; H 6.61; N 8.36. C₂₄H₂₂N₂. Calculated, %: C 85.17; H 6.55; N 8.28.

RESULTS AND DISCUSSION

Nano-TiCl₄ · SiO₂ [34, 35] as an efficient and reusable acidic catalyst is synthesized *via* reaction of nano-silica gel with TiCl₄ in chloroform at room temperature. Recently, our study about nano-TiCl₄ · SiO₂ structure led to more exact configuration containing SiO₂-TiCl₃ (19%) and SiO₂-TiCl₂-SiO₂ (81%) as Fig. 1.

The X-ray diffraction (XRD) patterns of nano-SiO₂ and nano-TiCl₄ · SiO₂ are shown in Fig. 2.

According to the Scherrer equation [36], the broadening of peaks implies the decrease in the crystalline size of nano-TiCl₄ · SiO₂. The XRD pattern of nano-SiO₂ has a strong peak in the 2θ value of 21.8024° with FWHM equal to 0.1771. According to the XRD pattern of nano-TiCl₄ · SiO₂, the values of 2θ and FWHM are shown in Table 1.

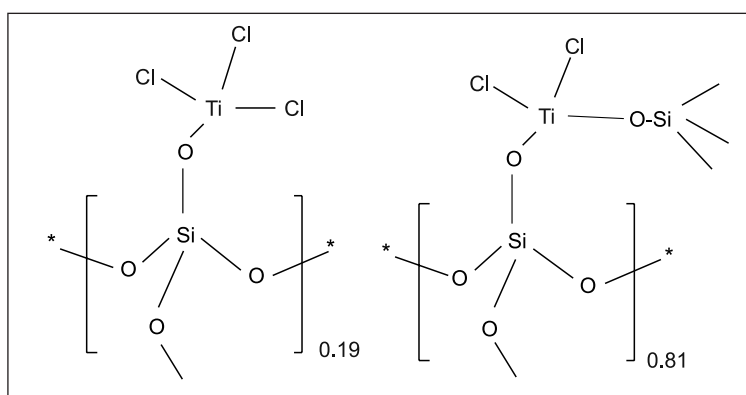


Fig. 1. Suggested structure for nano-TiCl₄ · SiO₂

Table 1. Nano-TiCl₄ · SiO₂ reflexes in XRD diffractogram

Entry	Pos. [°2 θ .]	FWHM [°2 θ .]
1	21.7587	0.3542
2	27.1424	1.6531
3	35.8287	0.4723
4	40.8394	1.1808
5	54.1881	1.1808
6	62.8214	0.7085
7	69.3466	2.3040

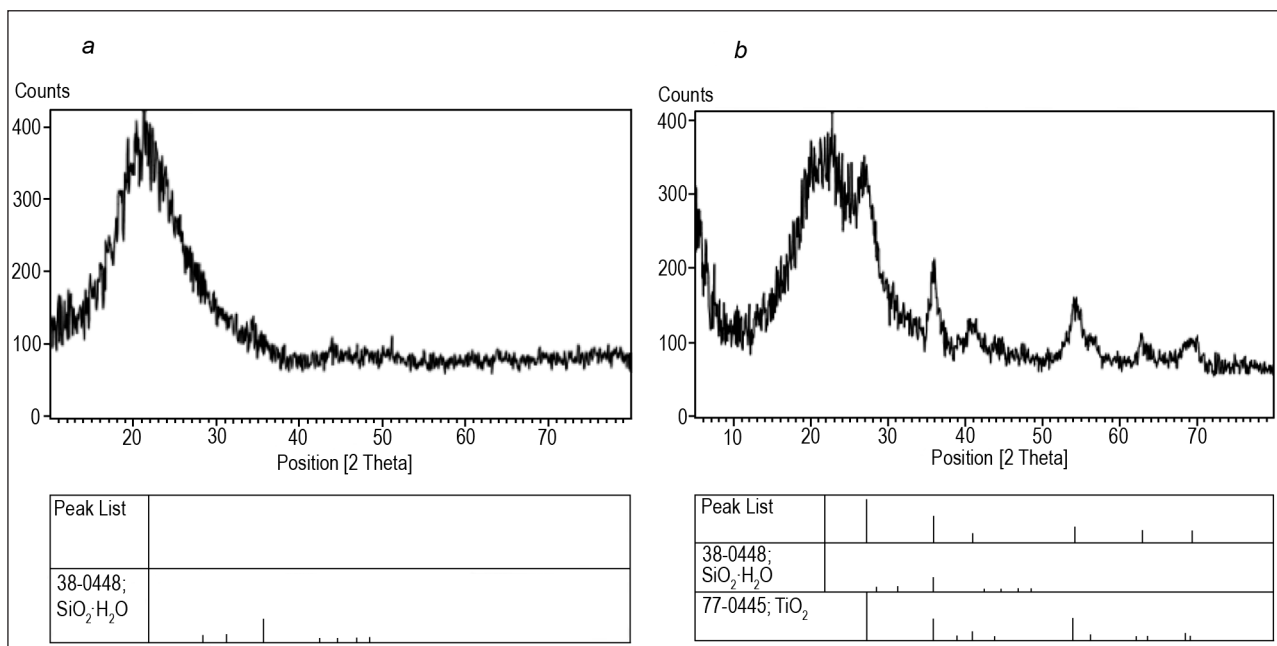


Fig. 2. X-ray diffraction (XRD) pattern of nano-SiO₂ (a) and nano-TiCl₄ · SiO₂ (b)

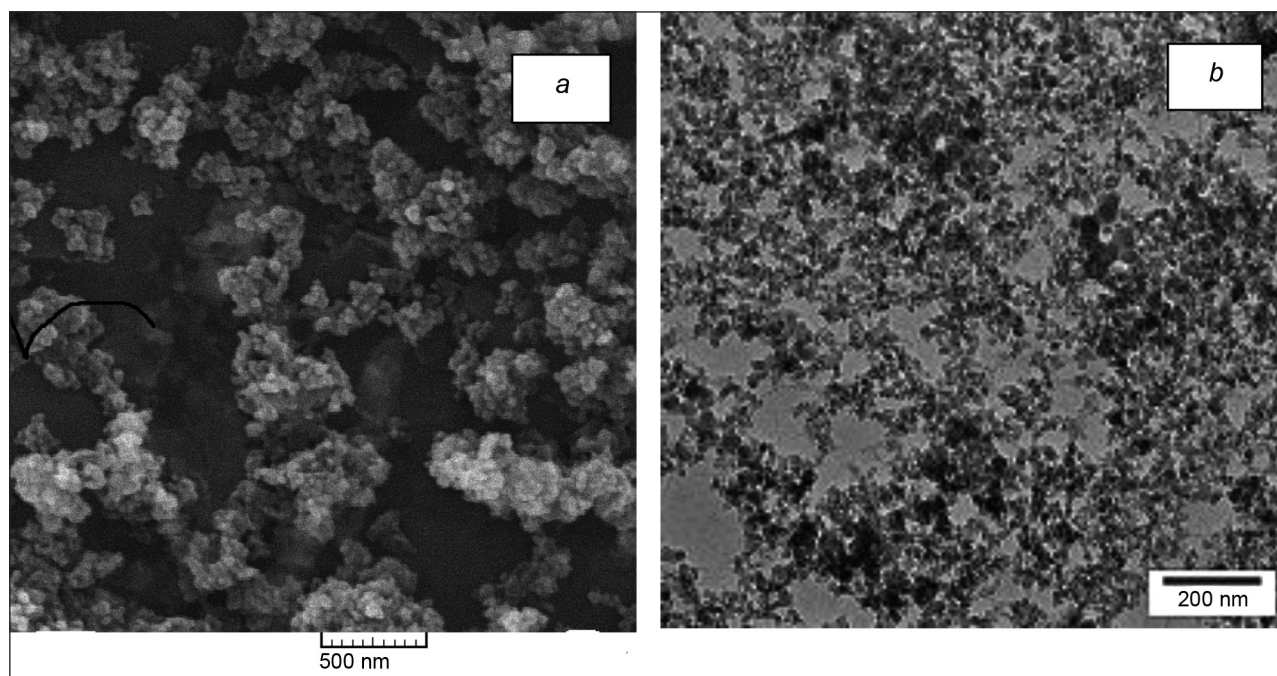


Fig. 3. a – SEM and b – TEM image of nano-TiCl₄ · SiO₂

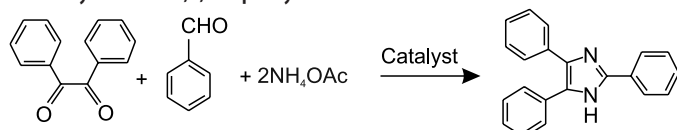
The scanning electron microscopy (SEM) and the transmission electron microscopy (TEM) image of nano-TiCl₄ · SiO₂ are shown in Fig. 3. The particle size in the TEM pattern is calculated between 14–20 nm by the GetData Graph program.

For investigation of the efficiency of nano-TiCl₄ · SiO₂ in preparation of 2,4,5-triphenylimidazoles, we examined the reaction of benzil (1 mmol), benzaldehyde (1 mmol) and ammonium acetate (2 mmol) as a model reaction. The reaction in different conditions in the presence of TiCl₄ · SiO₂

or nano-TiCl₄ · SiO₂ revealed that the best conditions were 0.1 g of TiCl₄ · SiO₂ or 0.04 g of nano-TiCl₄ · SiO₂ under solvent-free conditions at 110 °C (Table 2, entries 5 and 9).

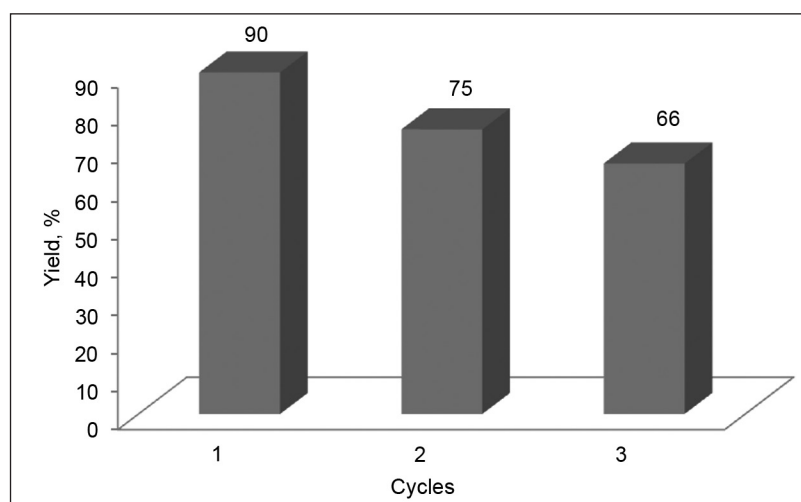
Once the scope of the reaction condition was established, the reusability of the catalyst was examined. After performing the reaction, the catalyst was separated, washed with acetone, dried and re-used up to 3 times in reaction without losing its activity (Fig. 4).

Next, benzil, ammonium acetate and various aldehydes were used as substrates for the synthesis of 2,4,5-trisubstituted

Table 2. Synthesis of 2,4,5-triphenyl-1*H*-imidazole in various conditions^a

Entry	Catalyst, g	Solvent/T °C	Time, h	Yield, %	[Ref]
1	TiCl ₄ · SiO ₂ (0.1)	Ethanol/r. t.	1.5	60	–
2	TiCl ₄ · SiO ₂ (0.1)	Methanol/r. t.	1.5	67	–
3	TiCl ₄ · SiO ₂ (0.1)	Iso-PrOH/80 °C	1.5	79	–
4	TiCl ₄ · SiO ₂ (0.1)	Ethanol / reflux	1.5	85	–
5	TiCl ₄ · SiO ₂ (0.1)	Solvent-free/110 °C	1	90	–
6	TiCl ₄ · SiO ₂ (0.1)	MM/Solvent-free ^b	0.5	30	–
7	TiCl ₄ · SiO ₂ (0.1)	Sonication/EtOAc ^c	0.4	62	–
8	TiCl ₄ · SiO ₂ (0.1)	MW/Solvent-free ^d	0.2	40	–
9	Nano-TiCl ₄ · SiO ₂ (0.04)	Solvent-free/110 °C	1	90	–
10	Nano-TiCl ₄ · SiO ₂ (0.04)	Solvent-free/110 °C	0.5	90	–
11	Nano-TiCl ₄ · SiO ₂ (0.02)	Solvent-free/110 °C	0.5	82	–
12	Nano-TiCl ₄ · SiO ₂ (0.04), 2nd run	Solvent-free/110 °C	1	75	–
13	Nano-TiCl ₄ · SiO ₂ (0.04), 3rd run	Solvent-free/110 °C	1	66	–
14	PEG-400 (1.5 g)	Solvent-free/110 °C	1	88	15
15	DABCO (0.7 mol %)	t-BuOH/65 °C	12–15	92	14
16	InCl ₃ · 3H ₂ O (10 mol %)	Methanol/r. t.	8.3	82	13
17	WD/SiO ₂ (20 wt %)	Solvent-free/140 °C	2	95	16
18	[EMIM]OAc (0.017)	Ultrasound/r. t.	0.5	87	18
19	K10 (0.01)	EtOH/Reflux	1.8	85	21
20	<i>n</i> -Bu ₄ NBr (0.032)	Iso-PrOH/82 °C	0.16	95	22
21	(NH ₄) ₆ Mo ₇ O ₂₄ · 4H ₂ O (0.12 g)	Solvent-free/MW	0.5	94	23
22	Nano-MgO (0.008 g)	Solvent-free/100 °C	0.6	94	24
23	KH ₂ PO ₄ (0.5 mol %)	EtOH/Reflux	0.7	93	25
24	InF ₃ (10 mol %)	Solvent-free/60 °C	0.3	90	26

Note: ^aThe ratio of benzaldehyde (mmol) : sodium acetate (mmol) : benzil (mmol) is 1 : 2 : 1, ^bUsing a mixer mill (MM 400) in 25 Hz frequency, ^cUsing a BANDELIN Sonopulse HD 3200 ultrasonic apparatus with power equal to 20 KHz, ^dUsing a microwave oven Kenwood, 1300 W.

Fig. 4. Reusability of nano-TiCl₄ · SiO₂ catalyst

ed imidazoles (Table 3). All the products were known and identified by spectroscopic and physical data comprised with literature.

As we studied the progress of reaction, in some cases we noticed the existence of a by-product in addition to main products. This compound might be generated because of

non-equivalent starting materials which could be formed via condensation of benzil with ammonia. Spectroscopic data (NMR) suggest a chemical structure which is shown as A₃ in Fig. 5. The results of ab initio calculations also show that this middle-product has a great stability. Its significant stability is attributed to an intra-molecular hydrogen bonding that

Table 3. Nano-TiCl₄ · SiO₂ catalyzed synthesis of 2,4,5-triaryl-1H-imidazoles^a

Entry	Products	Time, h	Yield ^b , %	m. p. °C		[Ref]
				Obtained	Reported	
1		0.5	90	274–275	275–276	18
2		0.5	91	253–255	–	–
3		0.5	92	226–228	227–228	22
4		0.5	89	209–211	207–208	18
5		1	88	197–199	197–199	18
6		1	89	261–263	260–262	21
7		1.5	84	174–175	174–175	20
8		1.5	89	264–265	263–265	19
9		2	85	228–230	230–231	29
10		2	87	268–269	269–271	23
11		2.5	89	237–238	239–242	18
12		2	–	228–229	227–229	8

Note: ^aThe ratio of benzil (mmol) : aldehydes (mmol) : ammonium acetate (mmol) : nano-TiCl₄ · SiO₂ (g) is 1 : 1 : 2 : 0.04, ^bIsolated yield.

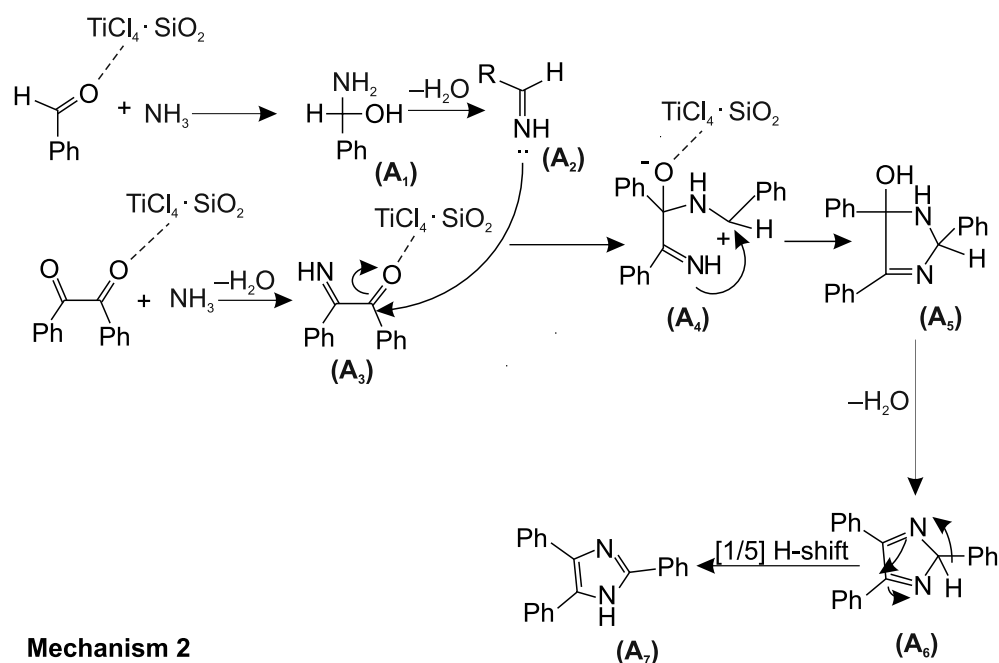
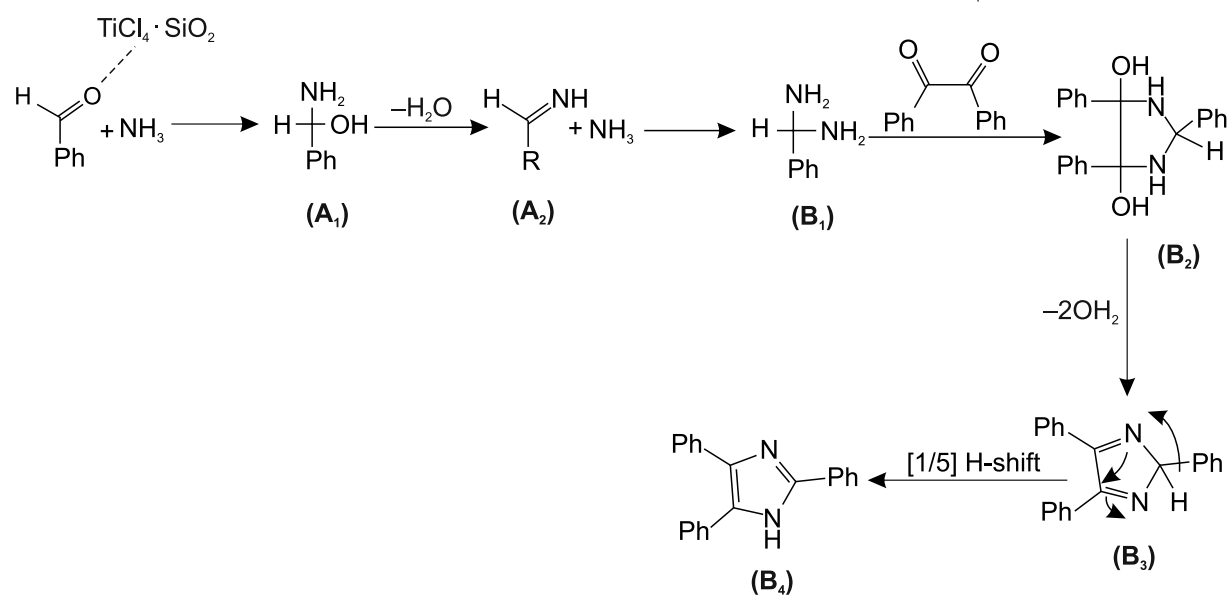
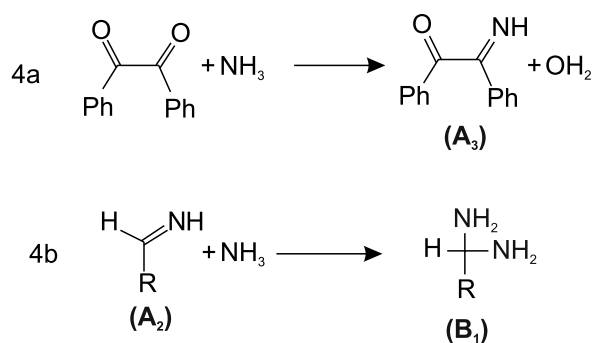
Mechanism 1**Mechanism 2**

Fig. 5. Two proposed mechanisms for the synthesis of 2,4,5-trisubstituted imidazoles

Fig. 6. Two mechanisms are the preparation of two species of A_3 and B_1

forms a pentagon ring. This middle-product A_3 is stable enough so that it remains as a stable compound at the end of reaction. The result of ab initio calculations is in agreement with spectroscopic data presented in the Supporting Information (Table S1 and Fig. S22). Previously, two proposed mechanisms for the synthesis of 2,4,5-trisubstituted imidazoles were reported in literature [37] in Fig. 5. The main difference between these two mechanisms is the preparation of two species of A_3 and B_1 . Reaction of ammonia with benzyl produces A_3 , whereas reaction of ammonia with the middle product (A_2) produces B_1 in Fig. 6. The changes of Gibbs free energies for the formation reactions of A_3 and B_1 presented in Fig. 6. are -11 and $+12$ kJ/mol, respectively, which are calculated at the MP2/GTMP2Large level of the theory in conjunction with B3LYP/6-31G(d) geometries and frequencies.

As a result, mechanism 1 that is presented in Fig. 5 has been found to be more probable for the synthesis of tri-substituted imidazole although the competitive mechanism 2 cannot be rolled out.

CONCLUSIONS

In conclusion, we have demonstrated a simple method for the synthesis of 2,4,5-trisubstituted imidazoles using nano- $TiCl_4 \cdot SiO_2$ as an eco-friendly, inexpensive, and efficient reagent. Short reaction times, high yield, simplicity of operation and easy work-up are some advantages of this method. The stabilities of middle-products in previously reported reaction mechanisms were studied by both experimental and theoretical methods.

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**VIENASTADIJINĖ 2,4,5-TRIPAKEISTŲ
1*H*-IMIDAZOLŲ SINTEZĖ, INICIJUOTA TiCl₄ · SiO₂
NANODALELIŲ: EKSPERIMENTINIS IR TEORINIS
TYRIMAS**

Santrauka

Nustatyta, kad TiCl₄ · SiO₂ nanodalelės švelniomis sąlygomis efektyviai katalizuoja 2,4,5-tripakeistų imidazolų sintezės reakcijas. Ši medžiaga buvo gauta reaguojant SiO₂ nanodalelėms su TiCl₄. Jos struktūra patvirtinta keliais fizikiniais metodais.